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Device to the examination more chemical and/or biological samples the invention relates to a device to the examination more chemical and/or biological samples with the help of optical mechanisms. Here for example in particular a confocal microscope can concern, a microscope.

Such investigation devices exhibit a lens to the observation of the sample. For example if a sample present in a sample carrier becomes from downside by a sample inertial soil transmissive for the corresponding observation radiation viewed with the help of the lens, then the given constellation of the refractive indexes, in particular with high-numerical lenses, affects adverse the course of the beam path.

Different refractive indexes arise with the transitions between the withdrawal lens of the lens and the ambient air as well as between the bottom of the sample carrier and the Mediums disposed between the lens and the sample inertial soil.

In particular with confocal microscopes, which become used in the Hochdurchsatzscreening, a very small focus must exist. This is required, since in the Hochdurchsatzscreening samples with small volumes in the pi range or smaller examined become. There the amount of the radiation (a collecting efficiency), delivered detected of the lens, by the sample, large influence on the measuring time has, must the aperture of the lens if possible high be. This is in particular important with the high throughput screening, since the measuring time represents one of the crucial parameters.

Usually becomes with the help of a pipette o. such. by hand an index matching liquid with a refractive index > 1 on the withdrawal lens of the lens applied. In particular in Hochdurchsatzscreening plants and fully automated microscopes o. A. this is extremely aufwändig, since the lens in short distance to a sample carrier, as a titer plate, disposed is. For applying the index matching liquid the lens must be gone back downward, so that an user with the help of a pipette o. A.

Index matching liquid on the withdrawal lens applied will can.

Subsequent one is driven near the lens the sample carrier, until the gap between the withdrawal lens of the lens and the outer surface of the sample carrier is filled by immersion medium. Likewise the lens can be more stationary and become the sample carrier moved.

An other disadvantage consists of the fact that with the examination of samples in titer plates, D. h. in sample carriers with a variety of individual samples, a relative movement between the lens and the titer plate, there each individual sample takes place by the lens to be started must or reverse. With this relative movement a part of the index matching liquid at the sample inertial lower surface always remains, so that filled after the examination several samples the gap between the withdrawal lens of the lens and the outer surface of the sample carrier cannot be any longer complete with index matching liquid.

Object of the invention is it to simplify a planning of index matching liquid with optical investigation devices.

The solution of the object made according to invention by a device in accordance with claim 1 and/or. a method in accordance with claim 16.

The device according to invention to the examination more chemical and/or biological samples exhibits according to invention supply means to automatic supplies of immersion medium. With the help of the supply means can between a sample carrier, which serves for the receptacle of the samples, and a withdrawal lens of a lens, which is provided to the observation of the sample, automatic immersion medium supplied become. The gap between withdrawal lens and lens is thus fillable during the observation of a sample always with immersion medium. Instead of a sample carrier also a means can to the receptacle and/or. to holding the sample carrier provided its. If necessary. the touched immersion medium then not the sample carrier, but a plate of the holder o. such.

There supplies automatic according to invention the made of immersion medium with the help of the supply means, is not an engage of user into the device, in particular Hochdurchsatzscreening plant or another automated device required. Rather the supply means can be so designed that also going back the lens, D. h. a removal of the lens of the outer surface of a sample inertial wall of the sample-inertial and/or. moving the sample carrier, not required is. It is with the device according to invention possible, in the measuring position of the lens, D. h. in the position, in which the lens is also during the examination of the sample, immersion medium to supply.

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The supply according to invention of immersion medium made preferably in such a manner that becomes formed between the lens and the outer surface of the sample inertial wall a thin film at immersion medium. Particularly prefered is it, if the gap width becomes here an in such a manner selected in dependence of the used immersion medium that the immersion medium becomes promoted due to of capillary forces into the gap.

Preferably the supply means exhibit for this a supply pipe connected with the lens. The supply pipe is in this embodiment of the lens held, so that an exit aperture of the supply pipe always a defined layer concerning. the withdrawal lens of the lens exhibits. The supply pipe is preferably in such a manner disposed that a rigid connection of the supply pipe with the lens can become realized. The exit aperture of the supply pipe is thus disposed outside of the beam path relevant for the measurement, so that the supply pipe does not throw shadow.

The exit aperture of the supply pipe is as close as possible at the withdrawal lens disposed. Preferably the distance is smaller smaller as 15 mm, in particular as 10 mm.

The cross-section area of the exit aperture, which is preferably flattened, is preferably smaller smaller as 1 mm2, in particular as 0.8 mm2.

In order to ensure uniform and as nonporous a one as possible jobs of the immersion medium on the withdrawal lens of the lens, is preferably the exit aperture of the supply pipe to a center of the withdrawal lens toward the lens offset disposed. This means with a lens pointing upward that the exit aperture of the supply pipe is disposed below one point of maximum of the withdrawal lens. Furthermore thereby is ensured that the supply pipe the sample carrier not touched.

To the promotion of the immersion medium the supply means exhibit for example a pump. With the preferably controllable pump it concerns in particular a controllable hose pump, which affects a tube connected with the supply pipe. Planning a hose pump has the advantage that parts of the pump, in particular no metal parts, with the immersion medium into contact to come and thus no impairment of the immersion

medium does not become by the pump caused.

An other possibility to the supply of the immersion medium is planning a reservoir, which over a fluid element, as a tube, with the supply pipe connected is. The reservoir is disposed opposite the exit aperture on a higher level, so that the immersion medium flows due to the Gewichtskraft toward the exit aperture. To the control of the withdrawal quantity as well as the frequency of the immersion withdrawal preferably a controllable valve can be provided in the fluid element.

By a pump or a reservoir, which can be alternatively also connected with a pump, it is possible to supply immersion medium for example to fixed predetermined times. Likewise is continuous supplies of immersion medium a possible.

With a preferable embodiment a Objektivkopf of the lens from a buffer is surrounded to the receptacle of excess immersion medium. A such buffer is in particular favourable with a continuous immersion medium supply. In particular due to the small gap between the withdrawal lens of the lens and the outer surface of the sample inertial wall the immersion medium film planned between the withdrawal lens of the lens and the outer surface of the sample carrier tears not off with a continuous or in predetermined temporal distances taking place immersion medium supply.

Preferably it preferably concerns during the buffer the entire Objektivkopf ambient collecting gutter. This can be in such a manner formed that her at its inner edge a sealing lip o. such. exhibits, so that the collecting gutter can be attached to conventional Objektivköpfe.

In order to be able to accomplish in particular prolonged series of investigations in Hochdurchsatzscreening plants, the buffer exhibits an exhausting opening, over which liquid immersion medium can become from the buffer discharged. By the exhausting opening the immersion medium can run off for example. Preferably the exhausting opening with a suction device is connected to the suction of the unnecessary immersion medium.

The gap planned between the withdrawal lens of the lens and the outer surface of the sample inertial wall exhibits with Hochdurchsatzscreening method preferably less as 1000 over, in particular less as 500, over, and particularly prefered less than 200 over. With such a small gap width tearing of the immersion medium off is avoided with continuous immersion medium supply. Furthermore the Mediums tear not off with a relative movement between the lens and the sample carrier, if a sufficient amount immersion medium is adjusted. Due to the capillary forces arising with one in such a manner small gap it is also possible to arrange those in such a manner managing described apparatus that the lens points downward.

Those managing described apparatus is in particular suitable to the use in confocal microscopes.

The invention relates to furthermore a method to the examination more chemical and/or biological samples, whereby it concerns an optical investigation procedure here in particular. In accordance with the invention process becomes a sample of female sample carriers a relative a lens disposed. The arrangement made in such a manner that is formed between an outer surface of a sample inertial wall and a withdrawal lens of the lens a gap. If the lens is disposed below the sample carrier, the gap runs thus between an underside of a sample inertial soil and the withdrawal lens. Subsequent one becomes the immersion medium automatic into the gap supplied. By automatic supplies the invention process is in particular favourable with continuous investigation procedures. In particular with Hochdurchsatzscreening method, with which a plurality of samples in short time intervals measured exhibits to become to have, the invention process significant saving of time as well as significant improvement of the test results.

Preferably the immersion medium becomes supplied over controllable supply means into the gap. Here it can act around a continuous, in regular intervals taking place or around a pure need-based supply of immersion medium.

The refractive index of the immersion medium preferably is > 1, in particular > 1,3, around numerical aperture of the lens of > 1 reach to be able.

Thereby an extremely small focus can become realized, which is necessary to a large resolution.

As immersion medium water or oil becomes preferably used.

The invention process exhibits the preferably additional step that the excess immersion medium becomes discharged.

Furthermore it is favourable to lead before supplies of the immersion medium a cleaning fluid into the gap. Thereby the outer lens of the lens as well as the sample inertial soil can become cleaned. As cleaning fluid for example alcohol can become used. Furthermore it is possible to use different immersion media and to clean before that supplies of a new immersion medium by supplies of cleaning fluid the withdrawal lens of the lens as well as the outer surface of the sample inertial wall. In order to accelerate a such procedure, it is possible to plan several supply means whereby by supply means for example a first immersion medium can become, by second supply means a cleaning fluid and by third supply means a second immersion medium supplied.

Furthermore it is possible to plan a Rückkopptung between that the withdrawal lens supplied and discharged amounts immersion medium. Thereby the amount at required immersion medium can become monitored. To the control that the withdrawal lens supplied amount at immersion medium as well as the discharged amount at immersion medium can be in the lead and/or the derivative a valve provided.

Subsequent one becomes the invention on the basis a preferable embodiment bottom reference on the lying close designs more near explained. Show: Fig. 1 a schematic side view of the device and Fig according to invention. 2 a schematic perspective view in Fig. 1 represented
Device.

The device according to invention exhibits a lens 10 with a vertical upward pointing withdrawal lens 12 in the illustrated embodiment.

Opposite the withdrawal lens 12 a sample carrier is 14 disposed, which takes up several samples 16. The underside of the sample carrier 14 is sealed by a transparent floor support wall 18, with which it concerns in the represented embodiment a sample inertial soil. With the help of the lens 10 16 examinations performed become in the individual samples.

The withdrawal lens 12 of the lens 10, with which it can concern for example also a protective gas or a Vorsatzlinse, is disposed opposite an outer surface of the sample carrier 10 in a distance. Thereby a gap is 22 formed between the withdrawal lens 12 and the outer surface 20 of the sample inertial wall 18.

With the help of supply means 24 an immersion medium supplied planned in a reservoir 26 becomes into the gap 22. For this the supply means exhibit a pump 28, which is 26 connected over a tube 30 with the reservoir. To the pump 28 a tube or a tube is 32 connected, which leads to a supply pipe 34. The end of the supply pipe 34 is a similar pipette tip formed and exhibits a flattened exit aperture 36. In order to avoid a decrease of the liquid column, a valve is 37 provided.

Around the distance of the exit aperture 36 of the supply pipe 34 concerning. the withdrawal lens 12 to adjust to be able, the tube is 32 held slidable in a clamper 38 in longitudinal direction. By the clamper 38 thus the layer of the exit aperture can become 36 relative the withdrawal lens 12 set. For this the clamper 38 can be for example also around a vertical axis longitudinal to the plane of the drawing tiltable disposed. The exit aperture 36 of the supply pipe 34 is in the represented embodiment 12 disposed below one point of maximum 40 of the withdrawal lens. The exit aperture 36 is thus in relation to the point of maximum 40 of the withdrawal lens 12 toward the lens 10 offset disposed.

The clamper 38 is by means of a screw 42 at the lens 10 an ambient kragenförmigen buffer 44 held. By the screw 42 an other adjustment of the clamper 38 and thus the exit aperture 36 of the supply pipe 34 can be made. The buffer 44 serves planned immersion medium 46 for the collection of between the Autrittslinse 12 and the sample carrier 14, if becomes 22 supplied over the supply means 24 for example too much or continuous immersion medium the gap.

The kragenförmige buffer 44 exhibits an exhausting opening 50 connected with a tube 48. Furthermore with the tube 48 a suction device connected can be.